HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

TEST PLAN

for

TALL OIL FATTY ACIDS AND RELATED SUBSTANCES

CAS No. 61790-I 2-3
CAS No. 65997-03-7
CAS No. 68955-98-6
CAS No. 68201-37-6
CAS No. 61790-44-I
CAS No. 61790-45-2

Submitted to the US EPA

By

The Pine Chemicals Association, Inc.
HPV Task Force
Consortium Registration #

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Test Plan For Tall Oil Fatty Acids and Related Substances

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Summary

The Pine Chemicals Association, Inc. (PCA) is sponsoring 36 HPV chemicals. This Test Plan addresses the following six chemicals, known collectively as Tall Oil Fatty Acids and Tall Oil Fatty Acid Salts:

61790-12-3, Fatty acids, tall-oil
65997-03-7, Fatty acids, tall-oil, low boiling
68955-98-6, Fatty acids, C16-C18 and C18 unsaturated, branched and linear
68201-37-6, Octadecanoic acid, branched and linear
61790-44-1, Fatty acids, tall oil, potassium salts
61790-45-2, Fatty acids, tall oil, sodium salts

These substances are all derived from or closely related to tall oil fatty acids, a substance obtained by the fractional distillation of crude tall oil, a by-product from the pulping of pine trees. Tall oil fatty acids and their derivatives are all complex mixtures (Class 2 substances) derived from a natural product. Each species of pine tree has a somewhat different mix of fatty acids, and even within a species, the mix of fatty acids could be influenced by the climate and local terrain.

While these are Class 2 substances, all the members of this group are similar in chemical composition, being predominantly C18 unsaturated and saturated fatty acids, or their salts. Thus, PCA has elected to treat the group as a category for purposes of the HPV program. Where applicable, PCA will conduct physical/chemical property and environmental fate testing on all six substances. However, a representative of the category will be used for ecotoxicity and *in vitro* mammalian toxicity testing. Due to the existence of available data on a representative chemical that satisfy the SIDS human health endpoints, no animal testing will be conducted.

Tall oil fatty acids (CAS# 61790-12-3) ("TOFA") has been selected as the representative substance in this group for testing for the additional SIDS data. This selection is based upon several factors, including the fact that TOFA represents by far the greatest production volume, with almost four times more TOFA manufactured than all other substances in this group combined. In addition, TOFA is the raw material from which all the other group members, except fatty acids, tall oil, low boiling, are derived. Consequently, test results obtained on TOFA will be most representative of the category. TOFA and the other members of this group are used primarily as raw materials for the production of other chemicals. For example, the largest use of TOFA is in the production of dimer acids, which are converted into coatings, adhesives and printing inks. TOFA salts are widely used as surfactants in liquid soaps. Other members of the group are used as intermediates in the production of isostearic acid.

PCA has reviewed existing data on these compounds. Available data show that TOFA has low toxicity. It is non-toxic following acute oral exposure and a number of repeat dose studies also show low toxicity. TOFA is not mutagenic in the Ames test. A full two-generation reproductive/developmental toxicity study has been performed, and there were no treatment-related effects. Thus, because adequate data already exist for most of the SIDS endpoints, particularly those requiring the use of animals, no additional testing in animals will be necessary.

A brief summary of the available data for the substances in this category, and the anticipated additional testing, is described below and in Table 1.

Physical/Chemical Properties

Physical and chemical properties will be determined when appropriate; however, many of the physical and chemical properties are either inappropriate or cannot be measured for these compounds:

- The melting point will not be determined because these substances will either not give a sharp melting point when heated or will decompose before they melt.
- Boiling points cannot be determined because these substances will decompose before they boil.
- Under ambient conditions, the vapor pressure of these chemicals is essentially zero and experimental measurement is not possible.
- The pH cannot be measured because the materials are not ionized. Moreover, pH cannot be determined for the salts, which are solids.
- Low solubility of these materials precludes measurement of adsorption/desorption to soil.
- The partition coefficients will be tested for the three substances where this has not been determined. Partition coefficient testing can yield a range of values representing the various components, rather than a single value representing the mixture.
- The water solubility of all six of the compounds in this grouping category will be determined.

Environmental Fate

With respect to the SIDS environmental fate endpoints:

- Determination of photodegradation is not relevant, since the vapor pressure of these compounds is essentially zero and they could not enter the atmosphere.
- Hydrolysis in water will not be determined for any of the six compounds in this category because the members of this category have low water solubility and lack a functional group that would be susceptible to hydrolysis.
- Biodegradation data will be generated for the two compounds for which data are not already available.

Ecotoxicity

- Existing ecotoxicity data are not reliable due to inconsistencies in, or artificial methods of, sample preparation. Consequently, using TOFA, acute toxicity to fish, daphnia and algae will be retested under conditions that maximize solubility, but reduce exposure to insoluble fractions, which may cause nonspecific toxicological effects.

Mammalian Toxicity

- For the SIDS human health endpoints, there are sufficient data on acute and repeat dose toxicity, *in vitro* genotoxicity in *Salmonella* (i.e., Ames test), and reproductive and developmental effects for tall oil fatty acid. Consequently, no additional testing for these endpoints will be conducted so no animals will be used.
- Because the required SIDS battery calls for two tests for mutagenicity, tall oil fatty acid will be tested for genotoxicity in an *in vitro* mammalian chromosome aberration test (OECD 473) both with and without metabolic activation.

Table 1
Matrix of Available Adequate Data and Proposed Testing
On Tall Oil Fatty Acids and Tall Oil Fatty Acid Salts*

Chemical and CAS #	Required SID Endpoints										
	Partition Coef.	**Water Sol.**	**Biodeg.**	**Acute Fish**	**Acute Daph.**	**Acute Algae**	**Acute oral**	**Repeat Dose**	**In vitro genetox (bact.)**	**In vitro genetox (non-bact)**	**Repro/ develop**
61790-12-3, Fatty acids, tall-oil	Adeq.	Test	Adeq.	Test	Test	Test	Adeq.	Adeq.	Adeq.	Test	Adeq./ Adeq.
65997-03-7, Fatty acids, tall-oil, low boiling	Adeq.	Test	Adeq.	C	C	C	C	C	C	C	C
68955-98-6, Fatty acids, C16-C18 and C18 unsat., branched & linear	Adeq.	Test	Adeq.	C	C	C	C	C	C	C	C
68201-37-6, Octadecanoic acid, branched and linear	Test	Test	Test	C	C	C	C	C	C	C	C
61790-44-1, Fatty acids, tall oil, potassium salts	Test	Test	Adeq.	C	C	C	C	C	C	C	C
61790-45-2, Fatty acids, tall oil, sodium salts	Test	Test	Test	C	C	C	C	C	C	C	C

Adeq. Indicates adequate existing data
Test Indicates proposed testing
C Indicates category read-down from existing or proposed test data on tall oil fatty acid.
* No testing will be conducted for melting point, boiling point, pH, vapor pressure, adsorption/desorption to soil, hydrolysis, and photodegradation, as described in the test plan. An attempt will be made to determine the pK_a of the sodium and potassium salts.

The Pine Chemicals Association, Inc. HPV Task Force includes the following companies:

Akzo Nobel Resins
Akzo Nobel – Eka Chemicals Incorporated
Arizona Chemical Company
Asphalt Emulsion Manufacturers Association
Boise Cascade Corporation
Champion International Corporation
Cognis Corporation
Georgia-Pacific Resins Inc.
Hercules, Incorporated
ICI Americas (Uniqema)
Inland Paperboard & Packaging, Inc.
International Paper Co.
Koch Materials Co
McConnaughay Technologies, Inc.
Mead Corp.
Packaging Corporation of America
Plasmine Technology, Inc.
Raisio Chemicals
Rayonier
Riverwood International
Smurfit – Stone Container Corporation
Westvaco
Weyerhaeuser Co.

The Task Force will be filing multiple test plans covering various chemicals. Not all members of the Task Force produce the substances covered by this test plan.

I. Description of Tall Oil Fatty Acids and Related Substances

The Pine Chemicals Association, Inc. (PCA) is sponsoring six HPV chemicals known collectively as Tall Oil Fatty Acids and Tall Oil Fatty Acid Salts. This group of chemicals consists of the following:

61790-12-3, Fatty acids, tall oil
65997-03-7, Fatty acids, tall oil, low boiling
68955-98-6, Fatty acids, C16 - C18 and C18 unsaturated, branched and linear
68201-37-6, Octadecanoic acid, branched and linear
61790-44-1, Fatty acids, tall oil, potassium salts
61790-45-2, Fatty acids, tall oil, sodium salts

These chemicals are all derived from or closely related to tall oil fatty acids (TOFA), a substance obtained by the fractional distillation of crude tall oil, a by-product from the pulping of pine trees. All the members of this group are similar in chemical composition, being predominantly C18 unsaturated and saturated fatty acids, or their salts. As a complex mixture derived from a natural product, TOFA and its derivatives are all considered Class 2 substances.

Fatty acids are present in the pine tree as glycerol esters and are saponified to sodium salts during the pulping process. These sodium salts are the major component of tall oil soap that is skimmed from spent pulping liquor and acidulated to form crude tall oil. Crude tall oil is then fractionally distilled at high temperatures under vacuum to yield several fractions, two of which are included in this group. Fatty acids, tall oil, low boiling (CAS# 65997-03-7) is the most volatile fraction, and TOFA is the second most volatile. The remaining members of this group are all derived from TOFA (Zinkel and Russell 1989).

A. Composition

Each species of pine tree has a somewhat different mix of fatty acids. Even within a species, the mix of fatty acids may be influenced by the climate and local terrain. Consequently, product specifications for these substances are not described in terms of chemical components, but in general terms such as acid number and iodine value, which are measures of aggregate chemical reactivity (Zinkel and Russell 1989). Provided below is some general information on the typical compositions of each of the six substances in this category.

1. Fatty Acids, Tall Oil (CAS# 61790-12-3)

The actual composition of a given tall oil fatty acid depends on factors such as the origin of the tall oil and the fractionation conditions used for its production. The composition of a typical tall oil fatty acid (TOFA) is shown in Table 2.

Table 2

Composition of a Typical Tall Oil Fatty Acid

Common Name	***Chemical Structure***	***Percent Composition***
Palmitic acid	$CH_3(CH_2)_{14}COOH$	1%
Stearic acid	$CH_3(CH_2)_{16}COOH$	2%
Oleic acid	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	48%
Linoleic acid	$CH_3(CH_2)_4CH=CH\text{-}CH_2CH=CH(CH_2)_7COOH$	35%
Conjugated linoleic acid[a]	$CH_3(CH_2)_XCH=CHCH=CH\text{-}(CH_2)_YCOOH$	7%
Other acids[b]		4%
Unsaponifiable matter		2%

a: x usually 4 or 5; y usually 7 or 8; but x + y = 12
b: 5,9,12-octadecatrienoic acid; linolenic acid; 5,11,14-eicosatrenoic acid; cis,cis-5,9-octadecadienoic acid; eicosadienoic acid; elaidic acid; cis-11 octadecanoic acid; C-20, C-22, C-24 saturated acids.

2. Fatty Acids, Tall Oil, Low Boiling (CAS# 65997-03-7)

The composition of tall oil, low boiling, better known as “tall oil heads,” is even more complex. As with TOFA, the composition of heads depends on the origin of the tall oil and the fractionation conditions. The TSCA Inventory defines tall oil heads as, *“the low boiling fraction obtained by the distillation of tall oil. Contains fatty acids such as palmitic, stearic, oleic and linoleic as well as neutral materials."* The neutral component is also complex, and contains small amounts of various terpenic hydrocarbons, alcohols, aldehydes, phenolics, lignin-derived materials, and other neutral materials. The composition of a typical tall oil heads is shown in Table 3.

Table 3

Composition of a Typical Tall Oil Heads

Common Name	***Chemical Structure***	***Percent Composition***
Palmitic acid	$CH_3(CH_2)_{14}COOH$	36%
Stearic acid	$CH_3(CH_2)_{16}COOH$	1%
Oleic acid	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	32%
Linoleic acid	$CH_3(CH_2)_4CH=CH\text{-}CH_2CH=CH(CH_2)_7COOH$	23%
Other acids[a]		8%
Unsaponifiable matter		10%

a: These are the same as indicated in Table 2 except the amounts of C20, C22, and C24 will be negligible.

3. Fatty Acids, C16-C18 and C18 Unsaturated, Branched and Linear (CAS# 68955-98-6)

Fatty acids, C16-C18 and C18 unsaturated, branched and linear (CAS# 68955-98-6) is better known as monomer acid. It is a co-product obtained in the production of dimer acid from TOFA. It has some of the characteristics of TOFA, except that it has a much lower level of unsaturation and also contains some branched chains. Monomer acid is a complex mixture of fatty acids; the major components are shown in Table 4.

Table 4

Composition of a Typical Monomer Acid

Common Name	***Chemical Structure***	***Percent Composition***
Palmitic acid	$CH_3(CH_2)_{14}COOH$	3%
Stearic acid	$CH_3(CH_2)_{16}COOH$	3%
Branched C18 acids		28%
Oleic acid (cis)	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	12%
Elaidic acid (trans)	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	24%
Other C18 acids[a]		24%
Unsaponifiable matter		1%

a: Probably cyclic acids of unknown structure.

4. Octadecanoic Acid, Branched and Linear (CAS# 68201-37-6)

Octadecanoic acid, branched and linear (CAS# 68201-37-6) is also known as hydrogenated monomer acid. It is an intermediate in the conversion of monomer acid into isostearic acid. Its composition is similar to the typical monomer acid shown in Table 4 except that all the acids are saturated.

5. Fatty acids, Tall Oil, Potassium Salt (CAS# 61790-44-1) and Sodium Salt (CAS# 61790-45-2)

Fatty acids, tall oil, potassium salt (CAS# 61790-44-1) and fatty acids, tall oil sodium salt (CAS# 61790-45-2) are simple salts of tall oil fatty acids. The salts are made by treating tall oil fatty acids with the appropriate base. As they are salts of a weak acid and a strong base, solutions of these salts are alkaline, with the pH depending on the concentration.

B. Commercial Uses of Tall Oil Fatty Acids and Tall Oil Fatty Acid Salts

Tall oil fatty acids (TOFA) is by far the most important member of this group from a commercial standpoint. The main use of TOFA is as a raw material for the production of a wide variety of other chemicals. TOFA has few, if any, uses in its unmodified form. The largest single use of TOFA is for the production of dimer acids that are then converted into coatings, adhesives, and printing inks. (Dimer acids will be addressed in another test plan.) Another important end use for tall oil fatty acids is in the production of alkyd resins that go into paints and printing inks. In all of these applications, TOFA improves the film forming properties and drying characteristics of the products into which it is formulated.

The salts of TOFA are widely used as surfactants. The sodium or potassium salts are used in liquid soaps for both industrial and household cleaning and disinfectant products. They also find uses in metal working fluids and in lubricants.

Tall oil heads are generally consumed for their fuel value. When the fatty acid content is sufficiently high, the heads can be used in some of the same markets as lower grades of TOFA.

Monomer acid is used in the production of isostearic acid, a liquid C18 acid. In addition, monomer acid can be used in some of the same applications as TOFA, such as soaps and lubricants.

Octadecanoic acid, branched and linear (hydrogenated monomer) is an intermediate in the production of isostearic acid from monomer acid and does not have any other specific commercial use.

C. Complexity of Analytical Methodology

All of the substances in this group are Class 2 substances. This, combined with the fact that fatty acids are essentially insoluble in water and decompose on heating at high temperature, create a variety of analytical issues. Gas chromatography of methylated derivatives is the accepted method for the analysis of the members of this group. However, the solubility of the free acids is very low (about 10 ppm). PCA has verified the reliability of the standard analytical methods at such low concentrations. Based on the method validation work to date, it appears that the analytical procedures will be adequate for the proposed testing.

II. Rationale for Selection of Representative Compound for Testing

TOFA (CAS# 61790-12-3) has been selected as the representative substance in this group for testing for the applicable SIDS ecotoxicity and *in vitro* mammalian genotoxicity tests, as shown in Table 5 (identical to Table 1). As also shown in Table 5, pertinent physical/chemical properties and environmental fate endpoints will

be determined for all six members of this group (for which data are not already available).

All the substances in this group are similar in chemical composition, being predominantly C18 unsaturated and saturated fatty acids, or their salts. The selection of TOFA as the substance to be tested is based on several factors. It has by far the greatest production volume, with almost four times more TOFA manufactured than all other substances in this group combined (i.e., 4, 64, and 28 times greater volume than the low boiling fraction, octadecanoic acid, and fatty acids, C16-18, respectively). EPA guidance suggests that testing the substance produced at the greatest volume as the representative chemical of a category would be appropriate. Clearly, TOFA fits this criterion. In addition, TOFA is the raw material from which all the other group members, except for tall oil heads, are derived.

Another criterion listed by EPA for grouping chemicals into a category is the use of the "family approach" of examining related chemicals when they are acids or acid salts. Although the salts of tall oil fatty acids have quite different physical characteristics, they are included in this group because they are quickly converted into the free acids when they are neutralized by acid or by dilution, as they would be under typical toxicity testing conditions. In summary, this group of chemicals fits the requirements of the EPA's HPV Challenge program for a chemical category, and TOFA is the most appropriate representative test material from this group.

III. Review of Existing Data and Development of Test Plan

PCA has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for the chemicals in this category. Considerable data are available that satisfy most of the HPV SIDS endpoints for this category. The availability of the data on the specific SIDS endpoints is summarized in Table 5 (identical to Table 1). Table 5 also shows data gaps that will be filled by additional testing, and areas where data from TOFA will be generalized to other category members. Because adequate data already exist for most of the SIDS endpoints, no additional testing in animals will be necessary.

Table 5
Matrix of Available Adequate Data and Proposed Testing
On Tall Oil Fatty Acids and Tall Oil Fatty Acid Salts*

Chemical and CAS #	Required SID Endpoints										
	Partition Coef.	**Water Sol.**	**Biodeg.**	**Acute Fish**	**Acute Daph.**	**Acute Algae**	**Acute oral**	**Repeat Dose**	**In vitro genetox (bact.)**	**In vitro genetox (non-bact)**	**Repro/ develop**
61790-12-3, Fatty acids, tall-oil	Adeq.	Test	Adeq.	Test	Test	Test	Adeq.	Adeq.	Adeq.	Test	Adeq./ Adeq.
65997-03-7, Fatty acids, tall-oil, low boiling	Adeq.	Test	Adeq.	C	C	C	C	C	C	C	C
68955-98-6, Fatty acids, C16-C18 and C18 unsat., branched & linear	Adeq.	Test	Adeq.	C	C	C	C	C	C	C	C
68201-37-6, Octadecanoic acid, branched and linear	Test	Test	Test	C	C	C	C	C	C	C	C
61790-44-1, Fatty acids, tall oil, potassium salts	Test	Test	Adeq.	C	C	C	C	C	C	C	C
61790-45-2, Fatty acids, tall oil, sodium salts	Test	Test	Test	C	C	C	C	C	C	C	C

Adeq. Indicates adequate existing data
Test Indicates proposed testing
C Indicates category read-down from existing or proposed test data on tall oil fatty acid
***** No testing will be conducted for melting point, boiling point, pH, vapor pressure, adsorption/desorption to soil, hydrolysis, and photodegradation. An attempt will be made to determine the pK_a of the sodium and potassium salts.

A. Evaluation of Existing Physicochemical Data and Proposed Testing

The basic physicochemical data required in the SIDS battery includes melting point, boiling point, pH, pK_a, vapor pressure, partition coefficient (K_{ow}), adsorption/desorption to soil, and water solubility.

Class 2 substances are composed of a complex mixture of substances and are often difficult to characterize. Tall oil fatty acids and their derivatives are Class 2 substances that are derived from natural sources. Their composition is variable and cannot be represented by a definite chemical structural diagram. Due to this "complex mixture" characteristic of tall oil fatty acids and their derivatives, some physical property measurements, such as partition coefficient and soil absorption/desorption, are not appropriate because the methodology used to

determine these properties will actually separate the Class 2 substances into their various component fractions. Rather than producing accurate measurements, the results of such testing are likely to be erroneous and difficult or impossible to interpret.

1. Melting Point

TOFA and the other non-salts in this grouping category are liquids at room temperature. In addition, a sharp melting point cannot be obtained due to the complex nature of these substances. Even though the two salts are solids under ambient conditions, heating them to determine the melting point would cause thermal decomposition. Consequently, the melting point will not be determined for any members of this grouping category.

2. Boiling Point

All of the non-salt members of this category are produced by high temperature, high vacuum distillation and are non-volatile at ambient temperatures. A boiling point has no significance because these materials will thermally decompose before they boil, when heated to high temperatures. The two salts in this group are solids. When heated to high temperatures, they will also thermally decompose before boiling. Accordingly, measurement of this property is inappropriate for all the substances in this category.

3. Vapor Pressure

Vapor pressures for the fatty acids at ambient temperatures are effectively zero, and their experimental measurement is inappropriate. The salt members of the group are solids and thus have no vapor pressure, so this end point cannot be measured. When dissolved in water their solutions will reflect the vapor pressure of the water rather than the salt, and therefore measurement of this property is inappropriate.

4. pH

The measurement of pH is based on the formation of hydrogen ions. The non-salt members of this group are weak organic acids that are not ionized in their normal state and so do not contain hydrogen ions. When mixed with water, they have minimal solubility (about 10 ppm) and consequently will generate few hydrogen ions and have a pH close to neutrality. Consequently, pH will not be measured.

The salt members of this group are solids, and pH measurement is not possible. When dissolved in water, they will give alkaline solutions (being salts of weak acids and strong bases), and the pH of these solutions will depend on the concentration of the salt in the solution. Consequently, experimental measurement of pH of these salts is inappropriate.

5. pK_a

Because all of the non-salt substances in this category are organic in nature and essentially insoluble in water, they will not disassociate and therefore determination of the pK_a would be inappropriate. For the two salts in this group, dissociation will occur. Consequently, an attempt will be made to determine the pK_a of the salts.

6. Adsorption/Desorption To Soil

Adsorption/desorption to soil measures the decrease in concentration when aqueous solutions of a chemical substance are in contact with different soil types at room temperature. The low solubility of the substances in this grouping category precludes testing for this endpoint. Consequently, adsorption/desorption to soil will not be undertaken on TOFA and related substances.

7. Water Solubility

The water solubility of all six compounds in this group will be determined using OECD (105).

8. Partition Coefficient

For the three members of this group for which partition coefficient data (i.e., K_{ow}) do not already exist (octadecanoic acid, branched and linear CAS# 68201-37-6; fatty acids, tall oil, potassium salts CAS# 61790-44-1; and fatty acids, tall oil, sodium salts CAS# 61790-45-2), the K_{ow} will be determined. As noted above, because all of these substances are Class 2 mixtures, the procedure (OECD 107) to determine the K_{ow} yields a number of separate K_{ow} values rather than a single value representative of the mixture. Existing data for TOFA reveals numerous K_{ow} values: at pH 2, seven K_{ow} values ranging from 4.4 to 8.3 and at pH 7.5, six K_{ow} values ranging from 3.6 to 7.4 reflecting the partition coefficients of the individual fatty acid constituents of this complex mixture. In this regard, it is reported that the partition coefficients for palmitic acid, stearic acid, oleic acid, and linoleic acid are 8.2, 8.2, 7.6, and 7.1, respectively. It should be noted that all of these fatty acids are well-recognized constituents of living organisms.

Summary of Physicochemical Properties Testing: The water solubility of all members of this group will be determined. The partition coefficients for the three members of this group for which there are no data will also be determined. While inappropriate for the free acids, the pK_a for the two salts will be measured, if possible. Tests for the melting point, boiling point, vapor pressure, pH, and adsorption/desorption to soil are inappropriate.

B. Evaluation of Existing Environmental Fate Data and Proposed Testing

The fate or behavior of a chemical in the environment is determined by the rates or half-lives for the most important transformation (degradation) processes. The basic environmental fate data covered by the HPV Program includes biodegradation, stability in water (hydrolysis as a function of pH) and photodegradation.

1. Biodegradation

Biodegradability can help to determine the fate of chemicals in the environment because it provides a measure for the potential of compounds to be degraded by microorganisms. Depending on the nature of the test material, several standard test methods are available to assess potential biodegradability.

Of the six chemicals in this group, four (TOFA; tall oil fatty acids, low boiling; fatty acids, C16-C18 and C18 unsaturated, branched and linear; and fatty acids, potassium salts) have existing data on the biodegradation endpoint. Biodegradation for octadecanoic acid, branched and linear and tall oil fatty acids, sodium salts will be determined.

2. Hydrolysis

Hydrolysis as a function of pH is used to assess the stability of a substance in water. Hydrolysis is a reaction in which a water molecule (or hydroxide ion) substitutes for another atom or group of atoms present in an organic molecule. If there is no group suitable to be displaced, then the organic compound is considered to be resistant to hydrolysis. None of the substances in the tall oil fatty acids category contains an organic functional group that might be susceptible to this physical degradative mechanism. Therefore, hydrolysis need not be measured.

In addition, low water solubility often limits the ability to determine hydrolysis as a function of pH. All of the tall oil fatty acids have very low solubility in water. Therefore, these materials are expected to be stable in water and it would be unnecessary to attempt to measure the products of hydrolysis. With respect to the fatty acid salts, since they exist in an aqueous medium they hydrolyze (ionize) immediately, but form stable species. Consequently, it would also be unnecessary to measure this endpoint for the fatty acid salts.

3. Photodegradation

Due to their low water solubility and lack of any vapor pressure, there is no opportunity for any of these chemicals to enter the atmosphere. Thus, photodegradation is irrelevant. In addition, based on the constituents in these complex mixtures, there is no reason to suspect that they would be subject to breakdown by a photodegradative mechanism. Consequently, this endpoint will not be determined for any of the substances in this category.

Summary of Environmental Fate Testing: Biodegradation data will be generated for two of the six compounds in this group for which data are not already available. Photodegradation and hydrolysis are inapplicable to these chemicals.

C. Evaluation of Existing Ecotoxicity Data and Proposed Testing

The basic ecotoxicity data that are part of the HPV Program includes acute toxicity to fish, daphnia and alga. While there are existing data on these endpoints for some of the substances in this grouping category, these data are conflicting and it is impossible to determine which, if any, of these findings is representative of true ecotoxicity. The inconsistencies in how water samples were prepared for testing these endpoints render these data inadequate. Consequently, acute toxicity to fish, daphnia and alga will be retested for TOFA under conditions that maximize the solubility under the specific test exposure conditions, but reduce exposure to insoluble fractions, which may cause nonspecific toxicological effects. In addition, the effect of both filtering, to further minimize nonspecific physical effects, and of reducing the pH to the lower end of the acceptable range for test organism survival, will also be investigated for changes in toxicological effects. The results of preliminary tests will be used to select the most appropriate test conditions for the definitive test for each species.

It should be noted that in EPA's latest guidance concerning the HPV Challenge Program (EPA 2000), there is a recommendation that chemicals with a log K_{ow} greater than 4.2 should be tested in a chronic toxicity to daphnia study (in place of the acute toxicity tests in fish and daphnia) and toxicity to algae. This is due to concerns about the possibility of bioconcentration for chemicals with a K_{ow} greater than 4.2. These concerns would not hold for TOFA and related chemicals since the high K_{ow} values are due to the various fatty acid constituents of these complex mixtures, which would not bioaccumulate. Consequently, the proposed acute ecotoxicity tests in daphnia, fish and algae are adequate to satisfy the requirements of the HPV program.

Summary of Ecotoxicity Testing: The acute toxicity of TOFA to fish, daphnia and algae will be tested under conditions that maximize its solubility, but reduce exposure to insoluble fractions, which may cause nonspecific toxicological effects.

D. Evaluation of Existing Human Health Effects Data and Proposed Testing

1. Acute Oral Toxicity

Acute oral toxicity studies investigate the effect(s) of a single exposure to a relatively high dose of a substance. This test is conducted by administering the test material to animals (typically rats or mice) in a single gavage dose. Harmonized EPA testing

guidelines (August 1998) set the limit dose for acute oral toxicity studies at 2000 mg/kg body weight. If less than 50 percent mortality is observed at the limit dose, no further testing is needed. A test substance that shows no effects at the limit dose is considered essentially nontoxic. If compound-related mortality is observed, then further testing may be necessary.

Summary of Available Acute Oral Toxicity Data

TOFA is non-toxic following acute oral exposure. TOFA was tested for acute oral toxicity in Sprague-Dawley rats. Animals received a single oral (gavage) dose of 10,000 mg/kg and were observed for 14 days. Parameters evaluated included clinical signs, mortality, body weight, and gross pathology. None of the animals died. One hour post-dosing, piloerection was observed in one male and abnormal stance was observed in one male and one female. By four hours, these effects had resolved. No body weight effects were observed. Gross necropsy revealed no treatment-related effects. The acute oral LD_{50} was greater than 10,000 mg/kg.

Summary of Acute Oral Toxicity Testing: TOFA has been tested for acute oral toxicity and found to be non-toxic (i.e., LD_{50} > 10,000 mg/kg) well above the guideline of 2000 mg/kg. Consequently, additional testing for this endpoint is not necessary.

2. Repeat Dose Toxicity

Subchronic repeated dose toxicity studies are designed to evaluate the effect of repeated exposure to a chemical over a significant period of the life span of an animal. Typically, the exposure regimen in a subchronic study involves daily exposure (at least 5 consecutive days per week) for a period of not less than 28 days or up to 90 days (i.e., 4 to 13 weeks). The HPV program calls for a repeat dose test of at least 28 days. The dose levels evaluated are lower than the relatively high limit doses used in acute toxicity (i.e., LD_{50}) studies. In general, repeat dose studies are designed to assess systemic toxicity, but the study protocol can be modified to incorporate evaluation of potential adverse reproductive and/or developmental effects.

Summary of Available Repeat Dose Toxicity Data

There are existing data that demonstrate a lack of toxicity for TOFA. Tall oil fatty acid (CAS #61790-12-3) was tested in a 90-day subchronic toxicity study in rats. The test material was administered to Charles River rats in the diet at concentrations 0, 5, 10, or 25% for 90 days. The approximate doses were 0, 2500, 5000, or 12,500 mg/kg/day. Parameters evaluated included clinical signs, mortality, body weight, body weight gain, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and microscopic pathology.

There were no deaths attributable to the test compound and no clinical signs were observed. Body weight and body weight gain were not affected by treatment, but

food consumption was slightly decreased at dietary levels of 10 and 25%. No changes in hematology, clinical chemistry or urinalysis parameters were measured at any dose level. At gross pathology, no treatment-related effects were noted. No consistent organ weight changes and no histopathological effects were reported. Based on these data, the No Observed Effect Level (NOEL) was 5% (approximately 2500 mg/kg/day).

Other subchronic studies for 28 and 40 days confirm the low toxicity of TOFA. In these studies, the only effect noted was depression of body weight gain at the highest doses tested.

Summary of Repeat Dose Toxicity Testing: TOFA has been tested for repeat dose toxicity in a 90-day study. In this study, the NOEL was approximately 2500 mg/kg/day, indicating that this compound has low toxicity. Other studies support this result. Consequently, no additional testing for this endpoint will be conducted.

3. Genotoxicity – In vitro

Genetic testing is conducted to determine the effects of substances on genetic material (i.e., DNA and chromosomes). The gene, which is composed of DNA, is the simplest functional genetic unit. Mutations can occur spontaneously or as a consequence of exposure to chemicals or radiation. Genetic mutations are commonly measured in bacterial and mammalian cells, and the HPV program calls for completing both types of tests.

Summary of Available Genotoxicity Data

TOFA was not mutagenic in the Ames assay. It was tested for mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations of 100, 333, 1000, 3333 and 10,000 μg/plate, with and without metabolic activation. No increases in mutation frequency were reported at any concentration, with or without metabolic activation. Tall oil fatty acid was not mutagenic in this assay. There are no *in vitro* genotoxicity data on mammalian cells.

Summary of Genotoxicity Testing: TOFA was not mutagenic in the Ames (bacteria) test. Consequently, no additional in vitro bacterial mutagenicity testing is necessary. The SIDS battery also includes an in vitro mammalian mutagenicity test. Therefore, TOFA will be tested for genotoxicity in an in vitro mammalian chromosome aberration test (OECD 473), both with and without metabolic activation.

4. Reproductive and Developmental Toxicity

Reproductive toxicity includes any adverse effect on fertility and reproduction, including effects on gonadal function, mating behavior, conception, and parturition. Developmental toxicity is any adverse effect induced during the period of fetal

development, including structural abnormalities, altered growth and post-partum development of the offspring.

The “toxicity to reproduction” aspect of the HPV Challenge Program can be met by conducting a reproductive/developmental toxicity screening test or adding a reproductive/developmental toxicity screening test to the repeated dose study (OECD 421 or OECD 422, respectively). The one-generation reproduction toxicity study (OECD 415) is a more comprehensive protocol for the study of the effect of a test material on reproduction and development that also meets the SIDS and the HPV Program requirements.

Summary of Reproductive/Developmental Toxicity Data

TOFA had no effects when tested for reproductive and developmental toxicity in Sprague-Dawley rats in a full two-generation study. The test compound was administered in the diet at concentrations of 0, 5 or 10% to 30 females/group and 15 males/group. The approximate doses were 0, 2500, or 5000 mg/kg/day. Males and females in the first generation (F_0) began treatment at 80 days of age and were mated at 100 days of age. Treatment of the F_0 animals continued through the weaning of the first generation (F_1). After weaning, the F_1 males and females were maintained on the treatment diet. At 100 days of age, they were mated and allowed to deliver pups (F_2).

There were no treatment-related effects on reproductive performance, or on any parameter measured in either the F_1 or F_2 pups. No treatment-related changes in fertility, viability, lactation, or gestation indices were observed. Hematology, clinical chemistry and urinalysis parameters were similarly unchanged, and there were no developmental effects in any F_1 or F_2 offspring. TOFA did not alter or otherwise affect the reproduction or development of rats in this study at doses as high as 10% (approximately 5000 mg/kg/day).

Summary of Reproductive/Developmental Testing: TOFA demonstrated no effects when tested for reproductive and developmental toxicity in a full two-generation study. Consequently, no additional reproductive/developmental toxicity testing is necessary.

References

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